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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,157	02/15/2002	Markus Pompejus	48684 DIV	9944

26474 7590 05/24/2004

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1350 CONNECTICUT AVENUE, N.W.
WASHINGTON, DC 20036

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,157	POMPEJUS ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/212,247.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/15/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1 and 4 are pending in the application.

[2] Applicants' amendment to the specification, filed April 21, 2004, is acknowledged. In view of the amendment, the objection to the specification as set forth in item [4] of the Office action mailed March 17, 2004 is withdrawn.

Election/Restriction

[3] Applicants' election with traverse of the invention of Group I, claims 1 and 4, drawn to an isolated or purified protein having the sequence of SEQ ID NO:2 and variants thereof including a variant having lysine at position 7 replaced with valine, filed April 21, 2004, is acknowledged.

Applicants traverse the restriction requirement by arguing that search and examination of any one of the claimed sequences will yield the information for examination of all other sequences and there is no undue burden on the examiner to search and examine all claimed sequences. Applicants' argument is not found persuasive.

Each of the claimed variants of SEQ ID NO:2 has a distinct amino acid sequence and no single amino acid sequence would render the others obvious to one of ordinary skill in the art, which is undisputed by applicants. Thus, as each of the claimed variants has a distinct amino acid sequence, a different sequence search is required for each of

the claimed variants of SEQ ID NO:2, thus requiring a serious burden on the examiner to search and examine all claimed variants.

[4] The requirement is still deemed proper and is therefore made FINAL.

[5] The non-elected subject matter of claim 4 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

[6] Claim 4 is being examined only to the extent the claim reads on the elected subject matter.

Information Disclosure Statement

[7] With the exception of US Patent 5,821,090 and EPO 0-405-370, none of the cited references of the IDS filed February 15, 2002 have been considered by the examiner as these references are not present in the instant application. The examiner requests that applicants supply copies of these references for consideration by the examiner.

Specification/Informalities

[8] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Phosphoribosyl-Pyrophosphate Synthetase Polypeptide".

[9] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1)

and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See pages 6 and 8-10 of the instant specification.

[10] The specification is objected to as there is no description of the drawings as required by 37 CFR 1.74. It is suggested that applicants provide a brief description of each figure in the specification. See MPEP 608.01(f).

Claim Objections

[11] Claim(s) 4 is objected to in the recitation of non-elected subject matter. It is suggested that, for example, applicants amend the claim so that it no longer recites non-elected subject matter.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[12] Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protein of SEQ ID NO:2 and a variant thereof having lysine at position 7 replaced with valine, does not reasonably provide enablement for all variants of SEQ ID NO:2 having phosphoribosyl-pyrophosphate synthetase activity as encompassed by the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: Claim 1 is so broad as to encompass a vast number of variants of SEQ ID NO:2 having phosphoribosyl-pyrophosphate synthetase activity, including all variants of SEQ ID NO:2 having any substitution(s), insertion(s), or deletion(s) of up to 15% of the amino acids of SEQ ID NO:2. The broad scope of claimed protein variants of SEQ ID NO:2 is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variants. In this case the disclosure is limited to SEQ ID NO:2 and a variant thereof having lysine at position 7 replaced with valine.

- The lack of guidance and working examples: The specification teaches only six substitutions of SEQ ID NO:2 that result in a protein having the desired phosphoribosyl-pyrophosphate synthetase activity (page 5, bottom of the specification). Other than these six substitutions, the specification fails to provide any guidance regarding those amino acids of the protein of SEQ ID NO:2 that can be altered with an expectation of obtaining a protein having the desired activity.

- The high level of unpredictability in the art: The amino acid sequence of a protein determines its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining

an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high level of unpredictability in altering the amino acid sequence of SEQ ID NO:2 with the expectation that the protein would have the desired phosphoribosyl-pyrophosphate synthetase activity.

- The state of the prior art supports the high level of unpredictability: The state of the art provides evidence for the high level of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no method for reasonably predicting the effects of even a *single* amino acid mutation on a protein. Such mutations may even completely alter a protein's activity. As a representative example of the teachings of Branden et al., Witkowski et al. (*Biochemistry* 38:11643-11650) teach that a single

amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

- The amount of experimentation required is undue: While methods of generating variants of a given polypeptide are known, e.g., site-directed mutagenesis, it is not routine in the art to screen for all proteins having a substantial number of substitutions, insertions, or deletions as encompassed by the instant claims.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the significant amount of experimentation required to make the full scope of claimed variant proteins, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. In this case, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is

unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Citation of Relevant Prior Art

[13] The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The closest relevant prior art to the claimed invention is Database GenBank Accession Number P38620, which discloses a polypeptide that is 82.5% identical to SEQ ID NO:2 and is disclosed as having phosphoribosyl-pyrophosphate synthetase activity (See Appendix A).

Conclusion

[14] Status of the claims:

- Claims 1 and 4 are pending.
- Claim 1 is rejected.
- Claim 4 would appear to be allowable if rewritten to overcome the objection set forth in this Office action. It is noted that claim 4 does not recite "isolated" or "purified" in the body of the claim. However, in light of the specification (page 5), it is clear that such a protein variant is generated by modification to the protein of SEQ ID NO:2 and would therefore not read on a naturally-occurring protein as the generation of such a variant implies the hand of the inventor.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652
05-14-04

APPENDIX A

```
RESULT 1
KPR2_YEAST
ID   KPR2_YEAST     STANDARD;      PRT;   318 AA.
AC   P38620;
DT   01-OCT-1994 (Rel. 30, Created)
DT   01-OCT-1994 (Rel. 30, Last sequence update)
DT   15-MAR-2004 (Rel. 43, Last annotation update)
DE   Ribose-phosphate pyrophosphokinase 2 (EC 2.7.6.1) (Phosphoribosyl
DE   pyrophosphate synthetase 2).
GN   PRPS2 OR PRS2 OR PRS OR YER099C.
OS   Saccharomyces cerevisiae (Baker's yeast).
OC   Eukaryota; Fungi; Ascomycota; Saccharomycotina; Saccharomycetes;
OC   Saccharomycetales; Saccharomycetaceae; Saccharomyces.
OX   NCBI_TaxID=4932;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   STRAIN=ATCC 44827 / SKQ2N;
RX   MEDLINE=95084630; PubMed=7992503;
RA   Carter A.T., Narbad A., Pearson B.M., Beck K.-F., Logghe M.,
RA   Contreras R., Schweizer M.;
RT   "Phosphoribosylpyrophosphate synthetase (PRS): a new gene family in
RT   Saccharomyces cerevisiae.";
RL   Yeast 10:1031-1044(1994).
RN   [2]
RP   ERRATUM.
RA   Carter A.T., Narbad A., Pearson B.M., Beck K.-F., Logghe M.,
RA   Contreras R., Schweizer M.;
RL   Yeast 11:191-191(1995).
RN   [3]
RP   SEQUENCE FROM N.A.
RA   Gerhardt H., Switzer R.L., Smith J.M., Hove-Jensen B.;
RL   Submitted (SEP-1993) to the EMBL/GenBank/DDBJ databases.
RN   [4]
RP   SEQUENCE FROM N.A.
RC   STRAIN=S288c / AB972;
RX   MEDLINE=97313264; PubMed=9169868;
RA   Dietrich F.S., Mulligan J.T., Hennessy K.M., Yelton M.A., Allen E.,
RA   Araujo R., Aviles E., Berno A., Brennan T., Carpenter J., Chen E.,
RA   Cherry J.M., Chung E., Duncan M., Guzman E., Hartzell G.,
RA   Hunicke-Smith S., Hyman R.W., Kayser A., Komp C., Lashkari D., Lew H.,
RA   Lin D., Mosedale D., Nakahara K., Namath A., Norgren R., Oefner P.,
RA   Oh C., Petel F.X., Roberts D., Sehl P., Schramm S., Shogren T.,
RA   Smith V., Taylor P., Wei Y., Botstein D., Davis R.W.;
RT   "The nucleotide sequence of Saccharomyces cerevisiae chromosome V.";
RL   Nature 387:78-81(1997).
CC   -!- CATALYTIC ACTIVITY: ATP + D-ribose 5-phosphate = AMP + 5-phospho-
CC       alpha-D-ribose 1-diphosphate.
CC   -!- PATHWAY: Utilized by both the de novo and the salvage pathways by
CC       which endogenously formed or exogenously added pyrimidine, purine,
CC       or pyridine bases are converted to the corresponding
CC       ribonucleoside monophosphates.
CC   -!- SIMILARITY: Belongs to the ribose-phosphate pyrophosphokinase
CC       family.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
CC   modified and this statement is not removed. Usage by and for commercial
CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; X75075; CAA52969.1; -.
DR   EMBL; X74414; CAA52436.1; -.
DR   EMBL; U18839; AAB64654.1; -.
DR   PIR; S37225; S37225.
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DR   HSSP; P14193; 1DKR.
DR   GermOnline; 139179; -.
DR   SGD; S0000901; PRS2.
DR   InterPro; IPR000842; PRPP_synthetase.
DR   InterPro; IPR000836; PRTransferase.
DR   InterPro; IPR005946; RibP_Ppkin.
DR   Pfam; PF00156; Pribosyltran; 1.
DR   TIGRFAMs; TIGR01251; ribP_PPkin; 1.
DR   PROSITE; PS00114; PRPP_SYNTHETASE; 1.
KW   Nucleotide biosynthesis; Transferase; Kinase; Magnesium;
KW   Multigene family.
FT   METAL       132    132       MAGNESIUM (POTENTIAL).
FT   METAL       134    134       MAGNESIUM (POTENTIAL).
FT   METAL       143    143       MAGNESIUM (POTENTIAL).
FT   METAL       147    147       MAGNESIUM (POTENTIAL).
SQ   SEQUENCE   318 AA;  34765 MW;  8B970E98084F5D71 CRC64;
```

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  Query Match            82.5%;  Score 1325;  DB 1;  Length 318;
  Best Local Similarity  80.7%;  Pred. No. 8.3e-93;
  Matches  255;  Conservative   35;  Mismatches   26;  Indels    0;  Gaps    0;

Qy          1 MSSNSIKLLAGNSHPDLAEKVSVRLGVPLSKIGVYHYSNKETSVTIGESIRDEDVYIIQT 60
              ||:|||||||||||| ||| :| ||||||||:||| |||||||||||||||||||||||||
Db          1 MSTNSIKLLAGNSHPGLAELISQRLGVPLSKVGVYQYSNKETSVTIGESIRDEDVYIIQT 60

Qy         61 GTGEQEINDFLMELLIMIHACRSASARKITAVIPNFPYARQDKKDKSRAPITAKLVAKML 120
              | || ||||||||||||:||||::|| |:|||||||||||||||||||||||||||:| :|
Db         61 GYGEHEINDFLMELLILIHACKTASVRRITAVIPNFPYARQDKKDKSRAPITAKLIANLL 120

Qy        121 ETAGCNHVITMDLHASQIQGFFHIPVDNLYAEPNILHYIQHNVDFQNSMLVAPDAGSAKR 180
              |||||:|||||||||||||||||||||| ||::|:||:   || |::||:|||| |||
Db        121 ETAGCDHVITMDLHASQIQGFFHIPVDNLYGEPSVLNYIRTKTDFNNAILVSPDAGGAKR 180

Qy        181 TSTLSDKLNLNFALIHKERQKANEVSRMVLVGDVADKSCIIVDDMADTCGTLVKATDTLI 240
               ::|:|||::|||||||||||||||||:|||||| |||:::|||||||||||||| |||:
Db        181 VASLADKLDMNFALIHKERQKANEVSRMLLVGDVAGKSCLLIDDMADTCGTLVKACDTLM 240

Qy        241 ENCAKEVIAIVTHGIFSGGAREKLRNSKLARIVSTNTVPVDLNLDIYHQIDISAILAEAI 300
              :: |||||||||||||| ||||| ||:|:||| |||||||||:|||  |:|||  :||||
Db        241 DHGAKEVIAIVTHGIFSGSAREKLINSRLSRIVCTNTVPVDLDLDIVDQVDISPTIAEAI 300

Qy        301 RRLHNGESVSYLFNNA 316
              |||||||||||| :|
Db        301 RRLHNGESVSYLFTHA 316
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